

Impact of Adolescent Obesity on Middle-Age Health of Women Given Data MAR

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Abstract

We analyze adolescent BMI and middle-age systolic blood pressure (SBP) repeatedly measured on women enrolled in the Fels longitudinal study (FLS) between 1929 and 2010 to address three questions: Do adolescent-specific growth rates in BMI and menarche affect middle-age SBP? Do they moderate the aging effect on middle-age SBP? Have the effects changed over historical time? To address the questions, we propose analyzing a growth curve model (GCM) that controls for age, birth-year cohort and historical time. However, several complications in the data make the GCM analysis non-standard. First, the person-specific adolescent BMI and middle-age SBP trajectories are unobservable. Second, missing data are substantial on BMI, SBP and menarche. Finally, modeling the latent trajectories for BMI and SBP, repeatedly measured on two distinct sets of unbalanced time points, are computationally intensive. We adopt a bivariate GCM for BMI and SBP with correlated random coefficients. To efficiently handle missing values of BMI, SBP and menarche assumed missing at random, we estimate their joint distribution by maximum likelihood via the EM algorithm where the correlated random coefficients and menarche are multivariate normal. The estimated distribution will be transformed to the desired GCM for SBP that includes the random coefficients of BMI and menarche as covariates. We demonstrate unbiased estimation by simulation. We find that adolescent growth rates in BMI and menarche are positively associated with and moderate the aging effect on SBP in middle age, controlling for age, cohort and historical time, but the effect sizes are at most modest. The aging effect is significant on SBP, controlling for cohort and historical time, but not vice versa.

KEY WORDS: longitudinal data; growth curve model; mixed model; hierarchical model; maximum likelihood.

1 Introduction

The Fels longitudinal study (FLS) collected the lifetime repeated measurements on growth, health and body composition of 2,567 participants enrolled in yearly cohorts of 20 to 35 from 1929 to 2010. The participants were scheduled to be examined every six months for the first 18 years and every two years for the rest of their life spans. Each examination took extensive anthropometric measurements and recorded a health inventory (Sun et al. 2007, 2008). Via a growth curve model (GCM) with person-specific growth trajectories, also known as a hierarchical, multilevel, random coefficients or linear mixed model (Raudenbush and Bryk 2002; Goldstein 2003), we link growth in adolescent BMI and person-specific (age at) menarche to the course of middle-age systolic blood pressure (SBP) for 835 female participants where 459 women were enrolled at birth producing 85% of the repeated measurements while others were family members, spouses and relatives. In this paper, we consider BMI and SBP as the biomarkers of obesity and health, respectively.

Figure 1 plots all observed BMI and SBP of the participants against age where 5,694 adolescent BMIs and 1,196 middle-age SBPs are nested within 552 and 436 individuals, respectively. It superimposes the scatterplots with person-specific longitudinal spaghetti plots. BMI and SBP are standardized to have mean 0 and variance 1. Every participant has at least one observation in adolescence or middle age. The spaghetti plots reveal that some growth patterns in BMI are higher overall, accelerate earlier or decelerate earlier than others. We analyze the impact of the growth patterns on progression of middle-age SBP. Because the 835 female participants consist of 98% European Americans and a tiny fraction of minority participants including African American, Asian, multiracial and other individuals and because the minority effect is not significant on either BMI or SBP outcome in preliminary analysis, we do not consider the race covariate.

The examination schedule implies that those enrolled at age 10 or earlier can have up to 18 adolescent measurements between 10 and 19 years of age and up to 10 middle-age measurements between 45 and 65 years of age, depending on how old they are as of 2010.

Some relatives, spouses and family members of the participants enrolled in the FLS during adolescence or later produced their measurements afterward. It is, however, unreasonable to take all these repeated measurements as complete data for analysis because only 18% of the 835 participants have at least one measurement in both adolescence and middle age. Instead, we realistically take the measurements at the time points of actual visits to a clinic for examination and menarche as complete data and assume data missing at random (MAR, Rubin 1976). As the spaghetti plots in Figure 1 show, the actual timings of examinations varied, and BMI appears semi-regularly measured while SBP looks more sparse and unbalanced.

Family relocations due to job transfers or newly acquired jobs, sickness of participants or family members accompanied to scheduled examinations, or other family emergencies or situations may have caused participants to miss scheduled examinations or attrite. During the scheduled examinations, 12% of the adolescents and 18% of adults failed to have their BMI and SBP measured, respectively, for some reasons. Menarche was either identified at a scheduled examination or obtained from participants' recollections, but missing otherwise. It seems plausible that the missing patterns are not related to missing values themselves. As a reviewer pointed out, however, it is possible for an adolescent to have a high BMI worsened since the last examination and fail to participate in the next scheduled examination because of embarrassment or anxiety. As the reviewer also commented, participants who have adolescent BMI measurements but who have no SBP measurement as adults are likely to be unhealthy and have high SBP in middle age. The missing BMI and SBP will be associated with missing probability to violate the MAR assumption. However, because the missing rates on BMI and SBP are modest, because 40% of the female participants having adolescent BMI measurements are younger than middle age as of 2010, and because most adolescents appear to have attended most follow-ups in the spaghetti plots, even if some missing BMI and SBP are NMAR, they will not seriously affect our analysis.

We leverage the FLS data collected longitudinally on individuals enrolled over time to estimate the age, cohort and historical time effects separately. In large-scale single cohort

studies such as the Dunedin Longitudinal Study and the Environmental-Risk Longitudinal Twin Study (Caspi et al. 2016; Moffitt et al. 2011), age and historical time are perfectly correlated. The confounded effects of age and childhood factors may explain only modest effect sizes of childhood risk factors on adult health outcomes reported (Felitti et al. 1998; Roberts et al. 2007; Moffitt et al. 2011; Caspi et al. 2016). On the contrary, age and cohort are perfectly collinear in a cross-sectional study of multiple birth year cohorts such as National Growth and Health Studies (Ren and Shin 2016). The multi-cohort FLS enables us to control for temporal, cohort and historical sources of SBP, and estimate the main effects of growth rates in adolescent BMI and menarche, and the growth rates-by-age and menarche-by-age interaction effects on middle-age SBP by a multilevel GCM. These effects may also change over cohorts and time.

Researchers have studied the impact of longitudinal growth patterns in childhood obesity on adult health or the effects of childhood covariates on a longitudinal adult outcome in linear and nonlinear mixed models (Eriksson et al. 1999; Law et al. 2002; Ferreira et al. 2005; Nooyens et al. 2007; Sabo et al. 2012; McLeod et al. 2018; Sabo et al. 2014). Kim et al. (2016) analyzed FLS longitudinal childhood BMI to predict the person-specific timing of the BMI rebound, and subsequently analyzed the impact of the timing on a longitudinal adult cardiac outcome. Sabo et al. (2017) analyzed the FLS childhood BMI to predict child-specific ages and BMIs at the BMI rebound and maximum BMI growth, and subsequently estimated the effects of the predicted childhood covariates on longitudinal adulthood blood pressure outcomes. These studies have assessed the impact of either adult characteristics on a longitudinal childhood outcome or childhood covariates on a longitudinal adult outcome.

In structural equation models (Bollen 1989), a longitudinal model for the repeated measurements of an outcome nested within individuals may be efficiently estimated by latent growth modeling where age variables are considered as fixed factor loadings and random coefficients are latent variables (Willett and Sayer 1994; MacCallum et al. 1997; Bauer 2003; Bollen and Curan 2006; Preacher et al. 2008; Grimm and Ram 2009; Ram and Grimm 2015).

Growth-mixture modeling extends the latent growth model to identify unobserved subpopulations exhibiting different growth trajectories (Wang and Bodner 2007). These approaches model longitudinal outcomes measured on a common set of time points.

In the joint modeling approach (Gueorguieva 2001; Ivanova et al. 2016), a mixture of discrete and continuous longitudinal outcomes may be modeled in a joint mixed model. Data MAR in the model may be imputed by univariate sequential regression models (Raghunathan et al. 2001), also known as multiple imputation by fully conditional specification (van Buuren et al. 2006; van Buuren 2011). A multilevel GCM given data MAR may also be efficiently estimated by maximum likelihood (ML) or Bayesian methods (Liu et al. 2000; Schafer and Yucel 2002; Goldstein and Browne 2002; Goldstein et al. 2009; Goldstein and Kounali 2009; Shin and Raudenbush 2007, 2010, 2020; Ren and Shin 2016). These approaches typically apply to longitudinal outcomes measured at a common set of time points.

In this paper, we estimate a nonstandard multilevel GCM for middle-age SBP that introduces challenges. First, the key covariates are unobservable adolescent-specific growth rates in BMI that have to be estimated from sample data. Sample average growth rates, for example, are unreliable measurements of the true growth rates that are known to introduce bias in the estimated effects of the growth rates (Lüdtke et al. 2008; Shin and Raudenbush 2010, 2020; Grilli and Rampichini 2011). Furthermore, missing data are substantial on BMI, SBP and menarche. Finally, longitudinal m_j BMIs in adolescence and n_j SBPs in middle age are measured at two separate sets of unbalanced time points nested within each person, and subjects may have measurements in either adolescence or middle age, or both. To handle missing data efficiently, we may express, as a special case of the joint modeling approach, a bivariate multilevel GCM for BMI and SBP and a linear model for menarche jointly where correlated person-specific random coefficients and menarche are multivariate normal and the variance covariance structure is appropriately constrained. Computationally efficient estimation of the joint model, however, involves derivation of new estimators and considerable amount of programming in a way that fully leverage the longitudinal structure.

Our method is tailored to the structure with one set of outcomes repeatedly measured at unbalanced time points during childhood and another set longitudinally measured at separate unbalanced time points as an adult within each individual, thereby achieving computational efficiency.

Viewing BMI, SBP, menarche and random coefficients as complete data, we analyze all observed data to estimate the joint model efficiently by ML via the EM algorithm (Dempster et al. 1977; Dempster et al. 1981; Shin and Raudenbush 2007). At convergence, we compute standard errors by the approximate Fisher score (Hedeker and Gibbons 1994; Raudenbush et al. 2000; Olsen and Schafer 2001). Subsequently, by the delta method (Casella and Berger 2002), we transform the estimated joint model to the desired GCM for SBP that includes the random coefficients of adolescent BMI and menarche as covariates. An alternative is to draw multiple imputation of completed data, including the random coefficients, from the estimated joint model and estimate the desired GCM given the multiple imputation (Shin and Raudenbush 2007). This approach requires a cumbersome extra step of multiple imputation. We choose the delta method that demanded less programming than the alternative. We will demonstrate unbiased estimation by simulation. Our findings may provide important policy implications to promote adult health based on juvenile obesity history.

Although FLS has not selected participants with respect to factors known to be associated with body composition, health, and other related conditions (Roche 1992), the participants are far from being randomly assigned to levels of key covariates, BMI growth rates and menarche. Furthermore, with adolescence far apart from middle age in time, there can be a number of confounders of the key covariates that we have not considered such as socioeconomic and environmental covariates unavailable in FLS. Consequently, the effect we mention in this paper is associational, not causal.

The Fels data set is not publically available. However, the data set analyzed in this paper will be available from the second author upon reasonable request. The next section introduces our model. Section 3 explains how to estimate the model and compute standard

errors given data MAR. Section 4 evaluates the accuracy and precision of the estimation by simulation. Section 5 presents analysis of the multi-cohort FLS sample data. The final section discusses the limitations and future extensions of the approach.

2 Model

Following Raudenbush and Bryk (2002), we express the repeated measurements of middle-age SBP R_{ij} and adolescent BMI C_{tj} for adult occasion i and adolescent occasion t within person j in a level-1 model

$$R_{ij} = A_{Rij}^T \beta_{Rj} + B_{Rij}^T \gamma_{R1} + \epsilon_{Rij}, \quad \epsilon_{Rij} \sim N(0, \sigma_{RR}), \quad (1)$$

$$C_{tj} = A_{Ctj}^T \beta_{Cj} + B_{Ctj}^T \gamma_{C1} + \epsilon_{Ctj}, \quad \epsilon_{Ctj} \sim N(0, \sigma_{CC}) \quad (2)$$

where $A_{Rij}^T \beta_{Rj}$ is a polynomial in adult age a_{ij} for vectors A_{Rij} of age terms and β_{Rj} of person-specific age effects (e.g. $A_{Rij}^T = [1 \ a_{ij}]$ and $\beta_{Rj}^T = [\beta_{R0j} \ \beta_{R1j}]$), B_{Rij} is a vector of known covariates (e.g. historical time) having fixed effects γ_{R1} , $A_{Ctj}^T \beta_{Cj}$ is a polynomial in adolescent age a_{tj} for vectors A_{Ctj} of age terms and β_{Cj} of adolescent-specific age effects (e.g. $A_{Ctj}^T = [1 \ a_{tj} \ a_{tj}^2]$ and $\beta_{Cj}^T = [\beta_{C0j} \ \beta_{C1j} \ \beta_{C2j}]$), B_{Ctj} is a vector of known covariates having fixed effects γ_{C1} (e.g. a_{tj}^3 and historical time), and occasion-specific random errors ϵ_{Rij} and ϵ_{Ctj} are independent for $i = 1, \dots, n_j$, $t = 1, \dots, m_j$ and $j = 1, \dots, J$. With adolescence and middle age far apart within each person, it appears reasonable that occasion-specific random errors ϵ_{Rij} and ϵ_{Ctj} are uncorrelated given the person-specific growth trajectories β_{Rj} and β_{Cj} and time-varying covariates. That is, given the covariates, SBP and BMI are dependent on each other only through the dependence between the trajectories.

The aging effects β_{Rj} on SBP vary between individuals according to a level-2 model

$$\beta_{Rj} = \Gamma_{R0} U_j + v_j, \quad v_j \sim N(0, \tau) \quad (3)$$

for a matrix Γ_{R0} of fixed effects; a vector $U_j = [W_{2j}^T \ Y_{2j}^T \ \beta_{Cj}^T]^T$ of known covariates W_{2j} (e.g. cohort), partially observed covariates Y_{2j} (e.g. menarche) and unobservable growth rates β_{Cj} in adolescent BMI; and a vector of random effects v_j independent of random errors and U_j . Conditional on v_j and covariates, SBP and BMI are independent. Although the growth trajectories may also vary differently across subpopulations to produce non-constant variances of random coefficients, for example, between males and females, we believe that the constant variance covariance matrix τ is plausible within our analysis of females, controlling for U_j . Equations (1) and (3) imply our desired GCM (Raudenbush and Bryk 2002)

$$R_{ij} = A_{Rij}^T \Gamma_{R0} U_j + B_{Rij}^T \gamma_{R1} + A_{Rij}^T v_j + \epsilon_{Rij} \quad (4)$$

for a matrix of fixed effects Γ_{R0} including the effects of aging moderated by U_j , the fixed effects γ_{R1} of B_{Rij} , and the random effects v_j of A_{Rij} independent of ϵ_{Rij} .

Estimation of GCM (4) is difficult because (R_{ij}, C_{tj}, Y_{2j}) are partially observed and because latent trajectories β_{Cj} are unobservable. We introduce efficient and unbiased estimation below. For a positive integer n , let I_n be an n -by- n identity matrix, 1_n be a vector of n unities, a diagonal matrix $\bigoplus_{i=1}^n A_i = \text{diag}\{A_1, \dots, A_n\}$, probability density function (pdf) $f(A)$ and conditional pdf $f(A|B)$.

3 Efficient Estimation

For efficient estimation by all observed data, we estimate the joint distribution of (R_{ij}, C_{tj}, Y_{2j}) MAR given known covariates. We view q random coefficients $\beta_{1j} = [\beta_{Rj}^T \ \beta_{Cj}^T]^T$ and p_2 variables Y_{2j} as level-2 complete data in a model $f(Y_{2j}^*)$

$$Y_{2j}^* = X_{2j} \gamma_2 + b_j, \quad b_j \sim N(0, T(\phi_T)) \quad (5)$$

for $Y_{2j}^* = [\beta_{1j}^T \ Y_{2j}^T]^T$, a matrix of covariates $X_{2j} = \text{diag}\{X_{21j}, X_{22j}\}$ having fixed effects $\gamma_2 = \begin{bmatrix} \gamma_{21} \\ \gamma_{22} \end{bmatrix}$, random effects $b_j = \begin{bmatrix} b_{1j} \\ b_{2j} \end{bmatrix}$ and $T(\phi_T) = \begin{bmatrix} T_{11} & T_{12} \\ T_{21} & T_{22} \end{bmatrix}$ having distinct elements ϕ_T for $X_{21j} = I_q \otimes W_{2j}^T$ and $X_{22j} = I_{p2} \otimes W_{2j}^T$. Each outcome in Y_{2j}^* may control for a different subset of W_{2j} as we do in Section 6. Let $\theta_2 = [\gamma_2^T \ \phi_T^T]^T$.

We aggregate $R_j = [R_{1j} \cdots R_{n_jj}]^T$ and $C_j = [C_{1j} \cdots C_{m_jj}]^T$ to view $Y_{1j} = [R_j^T \ C_j^T]^T$ and Y_{2j}^* as complete data and observed values of $Y_j = [Y_{1j}^T \ Y_{2j}^T]^T$ as observed data for person j , and estimate the joint model $f(Y_{1j}, Y_{2j}^*) = f(Y_{1j}|\beta_{1j})f(Y_{2j}^*)$ given known covariates by the EM algorithm. We aggregate Equations (1) and (2) as the level-1 model $f(Y_{1j}|\beta_{1j})$

$$Y_{1j} = A_{1j}\beta_{1j} + B_{1j}\gamma_1 + \epsilon_{1j}, \quad \epsilon_{1j} \sim N(0, \psi_j) \quad (6)$$

of person j where $A_{1j} = \text{diag}\{A_{Rj}, A_{Cj}\}$, $\beta_{1j} = [\beta_{Rj}^T \ \beta_{Cj}^T]^T$, $B_{1j} = \text{diag}\{B_{Rj}, B_{Cj}\}$, $\gamma_1 = [\gamma_{R1}^T \ \gamma_{C1}^T]^T$, $\epsilon_{1j} = [\epsilon_{Rj}^T \ \epsilon_{Cj}^T]^T$ and $\psi_j = \text{diag}\{I_{n_j}\sigma_{RR}, I_{m_j}\sigma_{CC}\}$ for $A_{Rj} = [A_{R1j} \cdots A_{Rn_jj}]^T$, $A_{Cj} = [A_{C1j} \cdots A_{Cm_jj}]^T$, $B_{Rj} = [B_{R1j} \cdots B_{Rn_jj}]^T$, $B_{Cj} = [B_{C1j} \cdots B_{Cm_jj}]^T$, $\epsilon_{Rj} = [\epsilon_{R1j} \cdots \epsilon_{Rn_jj}]^T$ and $\epsilon_{Cj} = [\epsilon_{C1j} \cdots \epsilon_{Cm_jj}]$. Let $\theta_R = [\gamma_{R1}^T \ \sigma_{RR}]^T$ and $\theta_C = [\gamma_{C1}^T \ \sigma_{CC}]^T$.

Equations (5) and (6) imply a linear mixed model

$$Y_j = X_j\gamma + Z_jb_j + \epsilon_j \quad (7)$$

for $Y_j = \begin{bmatrix} Y_{1j} \\ Y_{2j} \end{bmatrix}$, $X_j = \begin{bmatrix} X_{1j} & 0 \\ 0 & X_{22j} \end{bmatrix}$, $\gamma = \begin{bmatrix} \gamma_{y1} \\ \gamma_{22} \end{bmatrix}$, $Z_j = \begin{bmatrix} A_{1j} & 0 \\ 0 & I_{p2} \end{bmatrix}$ and $\epsilon_j = \begin{bmatrix} \epsilon_{1j} \\ 0 \end{bmatrix}$ where $X_{1j} = [B_{1j} \ A_{1j}X_{21j}]$ and $\gamma_{y1} = [\gamma_1^T \ \gamma_{21}^T]^T$. The parameters are $\theta = (\theta_R, \theta_C, \theta_2)$.

3.1 The EM Algorithm

We view complete data as (Y_{1j}, b_{1j}, Y_{2j}) for individual j , equivalent to $(\epsilon_{1j}, b_{1j}, b_{2j}) = (\epsilon_{1j}, b_j)$ given known covariates and θ for $\epsilon_{1j} = Y_{1j} - A_{1j}\beta_{1j} - B_{1j}\gamma_1$ and $b_{2j} = Y_{2j} - X_{22j}\gamma_{22}$. This approach simplifies expressions for the complete data likelihood, E-step, M-step and standard

error estimation. The complete data likelihood is

$$L(\theta|\epsilon_{1j}, b_j) = \prod_{j=1}^J g_j, \quad g_j = \left(\prod_{i=1}^{n_j} f(\epsilon_{Rij}|b_{1j}) \prod_{t=1}^{m_j} f(\epsilon_{Ctj}|b_{1j}) \right) f(b_j).$$

For the E step, we define matrix O_{2j} of ones and zeros to select observed data $Y_{o2j} = O_{2j}Y_{2j} \sim N(0, T_{22j})$ from Y_{2j} for $T_{22j} = O_{2j}T_{22}O_{2j}^T$ (Shin and Raudenbush 2007). Likewise, we define O_{Rj} , O_{Cj} and $O_{1j} = \text{diag}\{O_{Rj}, O_{Cj}\}$ to find observed data $R_{oj} = O_{Rj}R_j$ of length n_{oj} , $C_{oj} = O_{Cj}C_j$ of length m_{oj} , and $Y_{o1j} = O_{1j}Y_{1j} = [R_{oj}^T C_{oj}^T]^T$. Equation (7) implies $f(Y_{oj})$

$$Y_{oj} = X_{oj}\gamma + Z_{oj}b_j + \epsilon_{oj} \sim N(X_{oj}\gamma, V_{oj}) \quad (8)$$

where $Y_{oj} = [Y_{o1j}^T Y_{o2j}^T]^T$, $X_{oj} = \text{diag}\{X_{o1j}, X_{o22j}\}$, $Z_{oj} = \text{diag}\{A_{o1j}, O_{2j}\}$, $\epsilon_{oj} = [\epsilon_{o1j}^T 0^T]^T$ and $V_{oj} = Z_{oj}T Z_{oj}^T + \text{diag}\{\psi_{oj}, 0\}$ for $X_{o1j} = O_{1j}X_{1j}$, $X_{o22j} = O_{2j}X_{22j}$, $A_{o1j} = O_{1j}A_{1j}$, $\epsilon_{o1j} = O_{1j}\epsilon_{1j}$ and $\psi_{oj} = \text{diag}\{I_{n_{oj}}\sigma_{RR}, I_{m_{oj}}\sigma_{CC}\}$. For simplicity of notation, let $\mathcal{E}(A) = E(A|Y_{oj})$ and $\mathcal{V}(A) = \text{var}(A|Y_{oj})$. The observed-data joint model $f(Y_{oj})$ implies

$$b_j|Y_{oj} \sim N[\mathcal{E}(b_j), \mathcal{V}(b_j)], \quad \epsilon_{1j}|Y_{oj} \sim N[\mathcal{E}(\epsilon_{1j}), \mathcal{V}(\epsilon_{1j})] \quad (9)$$

for the E components $\mathcal{V}(b_{1j}) = \Delta_j^{-1}$, $\text{cov}(b_{1j}, b_{2j}|Y_{oj}) = \Delta_j^{-1}\Omega_{11j}^{-1}\Omega_{12j}$,

$$\begin{aligned} \mathcal{V}(b_{2j}) &= \Omega_{22j} - \Omega_{21j}(\Omega_{11j}^{-1} - \Omega_{11j}^{-1}\Delta_j^{-1}\Omega_{11j}^{-1})\Omega_{12j}, \\ \mathcal{E}(b_{1j}) &= \Delta_j^{-1} [A_{o1j}^T \psi_{oj}^{-1} d_{o1j} + \Omega_{11j}^{-1} E(b_{1j}|Y_{o2j})], \\ \mathcal{E}(b_{2j}) &= \Omega_{21j}\Omega_{11j}^{-1} [\mathcal{E}(b_{1j}) - E(b_{1j}|Y_{o2j})] + E(b_{2j}|Y_{o2j}), \\ \mathcal{V}(\epsilon_{1j}) &= \psi_j - \psi_j O_{1j}^T (\psi_{oj}^{-1} - \psi_{oj}^{-1} A_{o1j} \Delta_j^{-1} A_{o1j}^T \psi_{oj}^{-1}) O_{1j} \psi_j, \\ \mathcal{E}(\epsilon_{1j}) &= \psi_j O_{1j}^T \psi_{oj}^{-1} [d_{o1j} - A_{o1j} \mathcal{E}(b_{1j})] \end{aligned}$$

where $\Omega_{klj} = \text{cov}(b_{kj}, b_{lj}|Y_{o2j}) = T_{kl} - T_{k2}O_{2j}^T T_{22j}^{-1} O_{2j} T_{2l}$, $\Delta_j = A_{o1j}^T \psi_{oj}^{-1} A_{o1j} + \Omega_{11j}^{-1}$, $d_{o1j} = Y_{o1j} - X_{o1j}\gamma_{y1}$ and $E(b_{kj}|Y_{o2j}) = T_{k2}O_{2j}^T T_{22j}^{-1} d_{o2j}$ for $d_{o2j} = Y_{o2j} - X_{o22j}\gamma_{22}$ and $k, l = 1, 2$.

Given θ from the previous iteration, we compute the expected complete-data ML $\hat{\theta}$

$$\begin{aligned}\mathcal{E}(\hat{\gamma}_R) &= \gamma_R + \left(\sum_{j,i} B_{Rij} B_{Rij}^T \right)^{-1} \sum_{j,i} B_{Rij} \mathcal{E}(\epsilon_{Rij}), \quad \mathcal{E}(\hat{\sigma}_{RR}) = \frac{\sum_{j,i} \mathcal{E}(\epsilon_{Rij}^2)}{N_R}, \\ \mathcal{E}(\hat{\gamma}_C) &= \gamma_C + \left(\sum_{j,t} B_{Ctj} B_{Ctj}^T \right)^{-1} \sum_{j,t} B_{Ctj} \mathcal{E}(\epsilon_{Ctj}), \quad \mathcal{E}(\hat{\sigma}_{CC}) = \frac{\sum_{j,t} \mathcal{E}(\epsilon_{Ctj}^2)}{N_C}, \\ \mathcal{E}(\hat{\gamma}_2) &= \gamma_2 + \left(\sum_j X_{2j}^T T^{-1} X_{2j} \right)^{-1} \sum_j X_{2j}^T T^{-1} \mathcal{E}(b_j), \quad \mathcal{E}(\hat{T}) = \frac{\sum_j \mathcal{E}(b_j b_j^T)}{J}\end{aligned}$$

where $\sum_{j,i} = \sum_j \sum_i$, $N_R = \sum_j n_j$ and $N_C = \sum_j m_j$.

Let $Y_o = (Y_{o1}, Y_{o2}, \dots, Y_{oJ})$ be of length N_o . Then, the log-likelihood $l = l(\theta|Y_o) = \sum_j \log[f(Y_{o1j}|Y_{o2j})f(Y_{o2j})]$ is

$$\begin{aligned}l &= -\frac{1}{2} \sum_j \left\{ \log |\Omega_{11j}| + \log |\Delta_j| + n_{oj} \log \sigma_{RR} + \sum_t \log |\Sigma_{CCtj}| + d_{o1j}^T \psi_{oj}^{-1} [d_{o1j} - A_{o1j} \mathcal{E}(b_{1j})] \right. \\ &\quad \left. + E(b_{1j}|Y_{o2j})^T \Omega_{11j}^{-1} [E(b_{1j}|Y_{o2j}) - \mathcal{E}(b_{1j})] + \log |T_{22j}| + d_{o2j}^T T_{22j}^{-1} d_{o2j} \right\} - \frac{1}{2} N_o \log(2\pi).\end{aligned}$$

3.2 Standard Errors

At ML $\theta = \hat{\theta}$, we express the log-likelihood $l = \sum_j l_j$ and score $S = \sum_i S_j$ for

$$l_j = \log f(Y_{oj}) = \log \int_{\mathbb{R}^{k_j}} \int_{\mathbb{R}^q} g_j db_{1j} dY_{mj}, \quad S_j = \frac{\partial l_j}{\partial \theta} = \mathcal{E} \left(\frac{\partial \log g_j}{\partial \theta} \right)$$

where $Y_j = (Y_{oj}, Y_{mj})$ for k_j missing values Y_{mj} , and estimate $var(\hat{\theta}) = (\sum_j S_j S_j^T)^{-1}|_{\theta=\hat{\theta}}$ by the approximate Fisher score (Bock and Lieberman 1970; Raudenbush et al. 2000; Olsen and Schafer 2001). Let $E = \frac{\partial vec T}{\partial \phi_T^T}$ and $S_j^* = [S_{Rj}^{*T} S_{Cj}^{*T} S_{2j}^{*T}]^T$ for $S_{Rj}^* = \frac{\partial \log g_j}{\partial \theta_R}$, $S_{Cj}^* = \frac{\partial \log g_j}{\partial \theta_C}$ and $S_{2j}^* = \frac{\partial \log g_j}{\partial \theta_2}$. Based on the posterior distributions (9), we compute $S_j = \mathcal{E}(S_j^*)$ where

$$\mathcal{E}(S_{Rj}^*) = \begin{bmatrix} \frac{1}{\sigma_{RR}} \sum_i B_{Rij} \mathcal{E}(\epsilon_{Rij}) \\ \frac{1}{2} G_{Rj} \end{bmatrix}, \mathcal{E}(S_{Cj}^*) = \begin{bmatrix} \sum_t B_{Ctj}^T \Sigma_{CC}^{-1} \mathcal{E}(\epsilon_{Ctj}) \\ \frac{1}{2} G_{Cj} \end{bmatrix}, \mathcal{E}(S_{2j}^*) = \begin{bmatrix} X_{2j}^T T^{-1} \mathcal{E}(b_j) \\ \frac{1}{2} E^T vec(G_{2j}) \end{bmatrix}$$

for $G_{Rj} = \sum_i \mathcal{E}(\epsilon_{Rij}^2)/\sigma_{RR}^2 - n_j/\sigma_{RR}$, $G_{Cj} = \sum_t \mathcal{E}(\epsilon_{Ctj}^2)/\sigma_{CC}^2 - m_j/\sigma_{CC}$ and $G_{2j} = T^{-1}\mathcal{E}(b_j b_j^T)T^{-1} - T^{-1}$. Next, we transform the estimated joint model to the desired GCM by the delta method. Specifically, each parameter δ of the GCM is a function $g(\theta)$ of θ . We take the first-order Taylor-series approximation of $g(\hat{\theta})$ to estimate $\hat{\delta}$ and associated standard error.

To find the initial values of θ , we estimate two GCMs $f(R_{ij}, Y_{2j})$ and $f(C_{tj}, Y_{2j})$ given known covariates, implied from the joint model in Equations (1), (2) and (5), by efficient ML estimation (Shin and Raudenbush 2007); use estimated $f(R_{ij})$, $cov(R_{ij}, Y_{2j})$ and $f(C_{tj}, Y_{2j})$; and set $cov(R_{ij}, C_{tj})$ to zero. We estimated all models via a C program written by the first author¹, and simulated data and implemented the delta method within the R environment (R Core Team 2017) on a Dell XPS PC with Intel's i7 processor. In our experience with this estimation method so far, added random coefficients increase computational burden noticeably, but added time points do not.

4 Simulation Study

To assess our estimation, we simulate in sequence $W_j \sim \text{Bernoulli}(0.5)$ simulating a dummy indicator of a group of birth-year cohorts, $Y_{2j}|W_j \sim N(1 + W_j, T_{22})$ simulating the standardized menarche and a vector of four correlated random coefficients $\beta_{1j}|W_j, Y_{2j} \sim N(1_4 + 1_4 W_j + 1_4 Y_{2j}, T_{1|2})$ describing the linear growth trajectories of adolescent BMI and middle-age SBP at level 2 for $T_{22} = 1$, $\beta_{1j} = [\beta_{R0j} \ \beta_{R1j} \ \beta_{C0j} \ \beta_{C1j}]^T$, $T_{1|2} = \text{var}(\beta_{1j}|Y_{2j})$ having variances equal to 1 and covariances equal to 0.2 so that $W_{2j} = [1 \ W_j]^T$ in Equation (5). Given β_{1j} , we simulate SBP $R_{ij} \sim N(\beta_{R0j} + \beta_{R1j}a_{ij} + a_{ij}^2, 1)$ at age $a_{ij} = -9, -3, 3, 9$ centered at the midyear 55 of middle age in Equation (1) and BMI $C_{tj} \sim N(\beta_{C0j} + \beta_{C1j}a_{tj} + a_{tj}^2, 1)$ at age $a_{tj} = -4.5, -3.5, \dots, 3.5, 4.5$ centered at the midyear 14.5 of adolescence in Equation (2). Sample sizes are $n_j = 4$, $m_j = 10$ and $J = 500$ to reflect comparatively sparse middle-age SBP of FLS sample data analyzed in the next section. We simulate 1,000 data sets.

¹Convergence to ML is taken to be less than 10^{-6} in the difference between l values of two consecutive iterations.

Next, we draw missing values of R_{ij} , C_{tj} and Y_{2j} . For each simulated data set, we simulate missing indicators M_{Rij} , M_{Ctj} and M_{Y2j} of R_{ij} , C_{tj} and Y_{2j} , respectively, according to the following mechanisms

$$\text{logit}(p_{ij}) = \delta_0 + \delta_1 W_j + u_j, \quad \text{logit}(p_{tj}) = \delta_0 + \delta_1 W_j + v_j, \quad \text{logit}(p_j) = \delta_0 + \delta_1 W_j$$

for independent $u_j \sim N(0, 1)$ and $v_j \sim N(0, 1)$ such that $M_{Rij} \sim \text{Bernoulli}(p_{ij})$, $M_{Ctj} \sim \text{Bernoulli}(p_{tj})$ and $M_{Y2j} \sim \text{Bernoulli}(p_j)$. We simulated $\delta_0 = -1.5$ and $\delta_1 = -1.5$ to obtain $p_{ij} = 0.15$ (0.07 for $W_j = 1$ and 0.22 for $W_j = 0$), $\delta_0 = -2$ and $\delta_1 = -1$ to yield $p_{tj} = 0.11$ (0.07 for $W_j = 1$ and 0.16 for $W_j = 0$), and $\delta_0 = -1$ and $\delta_1 = 0.8$ to simulate $p_j = 0.36$ (0.45 for $W_j = 1$ and 0.27 for $W_j = 0$) on average. Missing values are MAR because M_{Rij} , M_{Ctj} and M_{Y2j} depend on known W_j . The missing rates closely reflect those of SBP, BMI and menarche in the FLS sample. As a result, 4.1, 17.0, 48.5, 126.1, and 304.4 individuals have 0, 1, 2, 3 and 4 SBPs observed, respectively, on average in the 1,000 observed data sets.

From the simulated bivariate distribution of BMI and SBP given Y_{2j} and W_j , we compute and show the implied simulated GCM (4) for SBP conditional on the random coefficients β_{C0j} and β_{C1j} of BMI, W_j and Y_{2j} under column heading “simulated” in Table 1. Next, we illustrate our approach for estimation of the joint model $f(R_{ij}, C_{tj}, Y_{2j} | a_{ij}, a_{tj}, W_j)$ in Equations (1), (2) and (5), i.e., Equation (7) by the EM algorithm and the subsequent delta method transforming the estimates to yield the estimated simulated GCM (4). We repeated our approach to estimate the simulated GCM (4) given each of the 1,000 simulated data sets to produce average estimates with associated average standard errors, biases and mean squared errors under heading “complete data EM” in Table 1. The average estimates are really close to the simulated parameters with the standard errors in parentheses, biases and mean squared errors comparatively very small.

Given partially observed data, we again obtain the average estimates of the simulated GCM (4) by our approach and list them under heading “observed data EM” in Table 1.

The average estimates are very close to the simulated parameters. Consequently, the biases appear very small near the counterparts under complete data EM. The standard errors and mean squared errors are 5% to 28% and 0 to 57% larger, respectively, than those of complete data EM to reflect added uncertainty due to missing data. Estimation of the joint model by the EM algorithm took only a few seconds to converge to ML in average 22 iterations.

5 Data Analysis

We now analyze the 835 female participants of FLS. Controlling for age, birth year cohort, and historical time as a visit year to a clinic for measurement, we estimate a multilevel GCM in Equation (4) for the effects of growth rates in adolescent BMI and menarche on middle-age SBP. The covariates may also strengthen or weaken the effect of aging on SBP. We discuss the statistical significance of an estimate at a significance level 0.05.

Table 2 summarizes sample data. At level 1, adolescent BMI and middle-age SBP range 12.32 to 46.61 and 75 to 210, missing 12% and 18% of the values, respectively. Age is centered at midyear 14.5 of adolescence (10 to 19 years of age) and 55 of middle age (45 to 65 years of age). Onset is 1 from diagnosis of a cancer and 0 otherwise. Visit years start from 1930 in adolescence and 1942 in middle age. We denote the last two digits of visit years ranging aa to bb by a dummy indicator “ $vyraa_bb$.” In middle age, $vyr42_50$ has a single SBP observed, and $vyr91_00$ and $vyr01_10$ show no difference in mean SBP by the t test so that we analyze $vyr42_60$, $vyr61_70$, $vyr71_80$, $vyr81_90$ and $vyr91_10$. In adolescence, we analyze $vyr30_40$ to $vyr01_10$ shown in Table 2. At level 2, menarche ranges 9 to 17 years of age, missing 37%. Birth year cohorts range 1889 to 1963 in middle age, and 1912 to 1997 in adolescence. We denote the last two digits of birth years ranging aa to bb by a dummy indicator “ $byraa_bb$.” A single SBP is observed in $byr89_00$, and no evidence of differences was found in mean SBP between $byr00_10$ and $byr10_20$ and in mean BMI between $byr80_90$ and $byr90_97$ by the t tests. Thus, we analyze byr_20 , referring to birth years from 1989 to 1920 in middle age and

from 1912 to 1920 in adolescence, to byr80_97 shown in Table 2. We standardize BMI and SBP to have mean 0 and variance 1, and center menarche at midpoint 13 years of age.

For efficient estimation of the GCM by all observed data, we estimate the joint distribution of R_{ij} =SBP, C_{tj} =BMI and Y_{2j} =menarche given known covariates in Equations (1), (2) and (5) for $A_{Rij}^T = [1 \ a_{ij}]$, $B_{Rij}^T = [\text{onset} \ \text{vyr42_60} \ \text{vyr61_70} \ \text{vyr71_80} \ \text{vyr81_90}]$ with the latest vyr91_10 as the reference level, $A_{Ctj}^T = [1 \ a_{tj} \ a_{tj}^2 \ a_{tj}^3]$, B_{Ctj} having adolescent onset and seven visit year indicators with the latest vyr01_10 as the reference, and W_{2j} having 1 for the intercept followed by the seven cohort indicators with the latest byr81_97 as the reference. In middle age, birth years range up to 1963 with 9 individuals in byr61_70 and no difference in mean SBP found between byr51_60 and byr61_70 so that we analyze byr51_70 as the reference and set the effects of later cohorts on β_{Rj} to zero. Preliminary analysis by efficient ML estimation of two hierarchical models $f(R_{ij}, Y_{2j})$ and $f(C_{tj}, Y_{2j})$ given known covariates implied by the joint model (Shin and Raudenbush 2007) not only provided the initial values of θ , but also enabled a series of likelihood ratio tests (LRT) that supported the first-degree polynomial $\beta_{R0j} + \beta_{R1j}a_{ij}$ in middle age and the third-degree polynomial $\beta_{C0j} + \beta_{C1j}a_{tj} + \beta_{C2j}a_{tj}^2 + \beta_{C3j}a_{tj}^3$ in adolescence (Stram and Lee 1994).

We attempted to simplify the joint model having 93 parameters, consisting of 63 fixed effects, 28 parameters in ϕ_T , and 2 error variances σ_{CC} and σ_{RR} . We identified and dropped eight BMIs and one SBP influential on the estimates by plotting the empirical Bayes estimates of random effects, and found some cohort effects different from zero on all random coefficients but β_{R1j} by LRT producing the p-value 0.31. With no cohort effects on β_{R1j} , we tested if the aging effect on SBP is randomly varying by testing $\text{var}(\beta_{R1j}) = 0$. We also tested if the cubic age effect on BMI is random by testing $\text{var}(\beta_{C3j}) = 0$. The large-sample distribution of the LRT statistics is a mixture $0.5\chi_6^2 + 0.5\chi_7^2$ (Stram and Lee 1994). The LRT statistics yield respective p-values 0.0002 and 0 in support of the random coefficients. Likewise, we found other age coefficients on BMI randomly varying.

Next, we transformed the full model to the desired GCM $f(R_{ij}|\beta'_{Cj}, Y'_{2j})$ given known

covariates where Y'_{2j} and β'_{Cj} are Y_{2j} and β_{Cj} centered at the respective birth-year means from $Y_{2j}^* - X_{2j}\gamma_2$ in Equation (5). Consequently, the cohort effects on β_{Rj} are marginal in the sense that they control for neither menarche nor BMI growth rates. The joint model also yields $f(Y_{2j})$ and $f(C_{tj}|Y'_{2j})$ given known covariates.

We show the estimated parameters of $f(Y_{2j})$, $f(C_{tj}|Y'_{2j})$ and $f(R_{ij}|\beta'_{Cj}, Y'_{2j})$ in Table 3. The estimates of $f(Y_{2j})$ under column heading “ $f(Y_{2j})$ ” reveal that the average age at menarche is 12.47 years old in byr81_97 (the intercept -0.53 plus the centered age 13 of menarche), younger than those in earlier cohorts although the cohort gaps are significant only in byr_20, byr51_60 and byr61_70. The estimates of $f(C_{tj}|Y'_{2j})$ in the subsequent column under heading “ $f(C_{tj}|Y'_{2j})$ ” reveal that for a 14.5 year-old adolescent, the expected BMI in byr81_97 is 0.67 standard deviations (SD) above the mean BMI and higher than those in earlier cohorts with the significant gaps in byr31_40 and later cohorts, and BMI decreases 0.39 SD for each year delayed in menarche on average controlling for onset and visit years. The linear age effect in byr81_97 is positive and higher than those in byr31_40 and byr51_60, and the quadratic and cubic age effects are negative and near zero in byr81_90, respectively, with no significant gaps across cohorts on average, controlling for the covariates in the model. The person-specific linear and quadratic growth rates β_{C1j} and β_{C2j} in BMI are positively and cubic rate β_{C3j} is negatively associated with menarche, ceteris paribus.

The estimated parameters of the desired GCM $f(R_{ij}|\beta'_{Cj}, Y'_{2j})$ in Equation (4) appear in the last column under heading “ $f(R_{ij}|\beta'_{Cj}, Y'_{2j})$ ”. For a 55 year-old woman, the growth rates in adolescent BMI and menarche are positively associated with SBP controlling for cohorts, onset and historical time, but these associations are statistically insignificant. The aging effect is positive and significant on SBP, but not significantly moderated by the growth rates in adolescent BMI and menarche, ceteris paribus. Women in earlier cohorts (earlier visit years) have higher (lower) expected SBP than do those in byr41_70 (vyr91_10), controlling for age, onset and historical time (cohorts). However, the effect sizes are at most modest. Overall, the aging effect is significant on SBP, controlling for cohorts and historical time, but

the cohort and temporal effects are not, controlling for age. To check if we might have found the aging effect by chance, we used the Bonferroni adjustment for testing 21 fixed effects to confirm that the aging effect is indeed significant.

Figure 2 graphs the predicted growths in adolescent BMI and middle-age SBP controlling for onset and historical time of measurement, respectively. Most strikingly, BMI is not only higher at the beginning of, but also grows faster throughout adolescence in *byr81_97* than in previous cohorts such that the differences between *byr81_97* and other cohorts grow to range 0.66 to 1.08 SDs at age 19. On the contrary, we see that the predicted progression of middle-age SBP barely changes across the cohorts up to *byr61_70*. This may be because the middle-age measurements in *byr81_97* are yet unavailable. When they become available, the impact of the rapid growth in adolescent BMI on middle-age health can be more pronounced.

Figure 3 exhibits the normal probability plots of the level-2 and -1 residuals from the joint model that produced the estimates in Table 3. Modest heavy tails are noticeable in some level-2 plots, in particular, for those of the random intercepts. This may be because as many as 296 adolescents and 139 adults have only zero to 2 repeated measurements observed in BMI and SBP, respectively, essentially downsizing effective sample sizes for the model fit. This may also be because of omitted covariates we were unable to control such as socioeconomic and environmental covariates unavailable in FLS. A nonnormal model more flexible with heavy tails might have resulted in an improved fit. Other than the moderate heavy tails, the residuals do not appear to deviate severely from the assumed model.

We repeated the analysis with an extra covariate, indicating if an individual was taking medication at the time of measurement, added to B_{Rij} and B_{Ctj} of the joint model. The total number of visits on medication happened at 22 adolescent and 53 middle-age occasions. Neither the significant effect of the covariate was found on either BMI or SBP, nor did the added covariate change the estimates in Table 3 in a notable way.

6 Discussion

We analyzed the repeated measurements of adolescent BMI and middle-age SBP nested within 835 female participants of FLS to estimate the lasting effects of growth rates in BMI and menarche, including the growth rates-by-age and menarche-by-age interaction effects, on SBP later in middle age via a multilevel GCM, controlling for onset of cancer, age, birth year cohort, and historical time of measurement. Estimation of the GCM was nonstandard and computationally intensive because BMI and SBP were repeatedly measured on two distinct sets of unbalanced time points nested within each participant, and missing values were substantial on BMI, SBP and menarche.

For efficient estimation by all observed data, we estimated the multilevel joint distribution of SBP, BMI and menarche assumed MAR given known covariates by ML via the EM algorithm. A series of likelihood ratio tests revealed that the coefficients of the linear, quadratic and cubic age terms on BMI and linear age on SBP vary randomly across individuals and that cohort effects are significant on menarche and random coefficients except the random slope of age on SBP. We transformed the estimated joint model to the desired GCM by the delta method. Because we analyzed FLS female participants who are mostly white, our findings are most appropriately applicable to European Americans. We illustrated unbiased estimation by our method via simulation.

The estimated mean growth trajectory in adolescent BMI is much higher among individuals born in 1981 to 1997 than those in earlier cohorts such that the mean differences are most striking, ranging 0.66 to 1.08 SDs on average, by age 19 as shown in Figure 2. Because middle-age measurements of those born in 1981 or later are not yet available, we are unable to show the impact on middle-age SBP. When they become available, we anticipate that the impact will strengthen quite remarkably.

We found only modest effect sizes of growth rates in adolescent BMI and menarche on SBP in our analysis. That may be because we have ignored an important family level. Because 376 family members and relatives who accompanied 459 participants enrolled at

birth to clinics for measurement were also measured, analysis of the repeated measurements of individuals nested within families would have resulted in more efficient estimates, which will be an important future analysis.

Because FLS started collecting socioeconomic covariates such as income and education quite recently since the year 2002, we could not control for the effects of such covariates. The omitted covariates may have contributed to the modest effect sizes we found. A valuable future research is to reanalyze the GCM, combining FLS with other longitudinal samples that have collected extensive socioeconomic covariates. Our missing data method can be extended to handle such analysis of multiple samples.

The FLS female sample comprises 1,196 occasions of 436 subjects to give 2.7 occasions per middle-age female. In addition, missing data are substantial on BMI, SBP and menarche. Consequently, the FLS female sample sizes may not have provided adequate power to detect the desired effects. Furthermore, adolescence and middle age may be too distant to reveal significant associations between BMI and SBP, possibly, due to confounders. In near future, we want to reanalyze the model in a way that increases sample sizes and also in a way that involves closer timeframes. For example, we may estimate the effects of growth rates in teenagers' obesity on an earlier adulthood outcome by the entire sample.

Adolescent obesity may also be too distant in time to reveal direct effects on middle-age health. What we have found in this paper may be the evidence of a lack of the direct effects of growth rates in adolescent obesity on middle-age health, and important mediators may exist in closer future. For example, it is plausible that the effects of adolescent obesity on middle-age health are mediated by a near-future health outcome in earlier adulthood. Although we have illustrated the impact of a univariate BMI in adolescence on a univariate SBP in middle age, extension to multivariate health outcomes is straightforward.

Under our current model, we assumed constant variances σ_{RR} and σ_{CC} of occasion-specific or within-person random errors of middle-age SBP and adolescent BMI, respectively. In near future, we want to estimate non-constant error variances σ_{RRj} and σ_{CCj} of person j such

that the person-specific random coefficients of SBP are correlated with the within-person variances $\log(\sigma_{RRj})$ and $\log(\sigma_{CCj})$ (Hedeker et al. 2008). We will also consider the non-constant variances of the SBP and BMI growth trajectories, for example, across males and females in an extended FLS analysis.

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Conflict of Interest

The authors have declared no conflict of interest.

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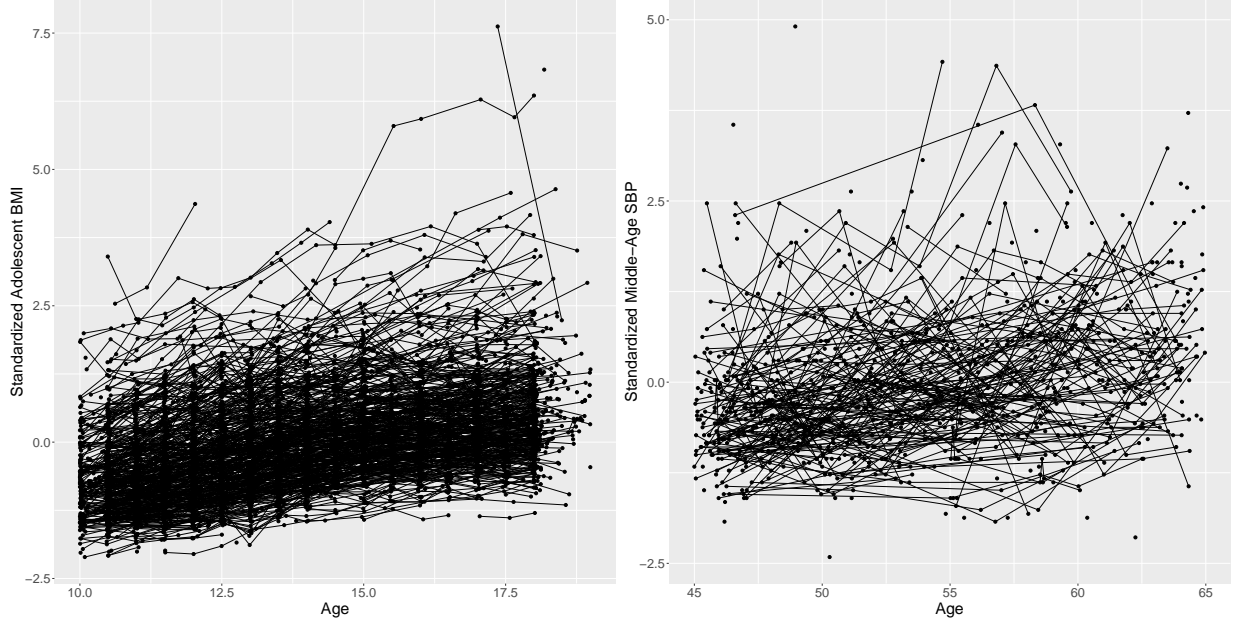


Figure 1: Scatter and spaghetti plots superimposed for the unbalanced repeated measurements of adolescent BMI and middle-age SBP against age from 835 FLS female participants enrolled over time across multiple birth year cohorts.

Table 1: Model (4) simulated 1,000 times for $n_j = 4$, $m_j = 10$ and $J = 500$ with simulated parameters under heading simulated. Complete data EM and observed data EM list the average estimates and standard errors (se) by the EM algorithm, bias and mean squared errors (mse) given completely observed data and data MAR, respectively.

	simulated	complete data EM		observed data EM	
		estimate (se)	bias, mse	estimate (se)	bias, mse
1	0.67	0.66 (0.11)	-0.005, 0.012	0.66 (0.13)	-0.004, 0.015
W_j	0.67	0.67 (0.13)	0.007, 0.016	0.67 (0.14)	0.008, 0.020
β_{C0j}	0.17	0.17 (0.05)	0.001, 0.003	0.17 (0.06)	0.000, 0.004
β_{C1j}	0.17	0.17 (0.05)	0.001, 0.003	0.17 (0.06)	0.000, 0.003
Y_{2j}	0.67	0.66 (0.08)	-0.003, 0.007	0.67 (0.11)	-0.001, 0.011
a_{ij}	0.67	0.66 (0.10)	-0.004, 0.010	0.66 (0.10)	-0.005, 0.011
$a_{ij}W_j$	0.67	0.67 (0.12)	0.004, 0.013	0.67 (0.12)	0.004, 0.014
$a_{ij}\beta_{C0j}$	0.17	0.17 (0.05)	-0.001, 0.002	0.17 (0.05)	-0.001, 0.003
$a_{ij}\beta_{C1j}$	0.17	0.17 (0.05)	0.002, 0.002	0.17 (0.05)	0.001, 0.002
$a_{ij}Y_{2j}$	0.67	0.66 (0.08)	-0.002, 0.005	0.67 (0.09)	0.000, 0.007
a_{ij}^2	1.00	1.00 (0.00)	0.000, 0.000	1.00 (0.00)	0.000, 0.000
τ_{00}	0.93	0.92 (0.08)	-0.011, 0.006	0.92 (0.09)	-0.011, 0.008
τ_{01}	0.13	0.14 (0.05)	0.002, 0.002	0.13 (0.06)	0.002, 0.003
τ_{11}	0.93	0.92 (0.06)	-0.009, 0.004	0.92 (0.07)	-0.009, 0.004
σ_{RR}	1.00	1.00 (0.05)	-0.002, 0.002	1.00 (0.05)	-0.002, 0.003

Table 2: FLS female data summary for analysis. “vyr” and “byr” stand for visit year and birth year, respectively.

Level		Mean(sd, missing)		Mean(sd, missing)	
1	SBP	119.50 (18.44,18%)	BMI	19.74 (3.53,12%)	
	age	-1.21 (5.71, 0%)	age	-0.56 (2.47, 0%)	
	onset	0.10 (0.30, 0%)	onset	1E-3 (0.03, 0%)	
	vyr42_60	0.07 (0.26, 0%)	vyr30_40	0.03 (0.18, 0%)	
	vyr61_70	0.17 (0.38, 0%)	vyr41_50	0.19 (0.40, 0%)	
	vyr71_80	0.10 (0.30, 0%)	vyr51_60	0.16 (0.36, 0%)	
	vyr81_90	0.07 (0.26, 0%)	vyr61_70	0.16 (0.36, 0%)	
	vyr91_10	0.58 (0.49, 0%)	vyr71_80	0.18 (0.38, 0%)	
			vyr81_90	0.11 (0.31, 0%)	
			vyr91_00	0.11 (0.31, 0%)	
			vyr01_10	0.07 (0.25, 0%)	
2	menarche	12.73 (1.20,37%)			
	byr_20	0.20 (0.40, 0%)			
	byr21_30	0.06 (0.24, 0%)			
	byr31_40	0.12 (0.33, 0%)			
	byr41_50	0.11 (0.32, 0%)			
	byr51_60	0.17 (0.38, 0%)			
	byr61_70	0.12 (0.32, 0%)			
	byr71_80	0.07 (0.26, 0%)			
	byr81_97	0.14 (0.35, 0%)			

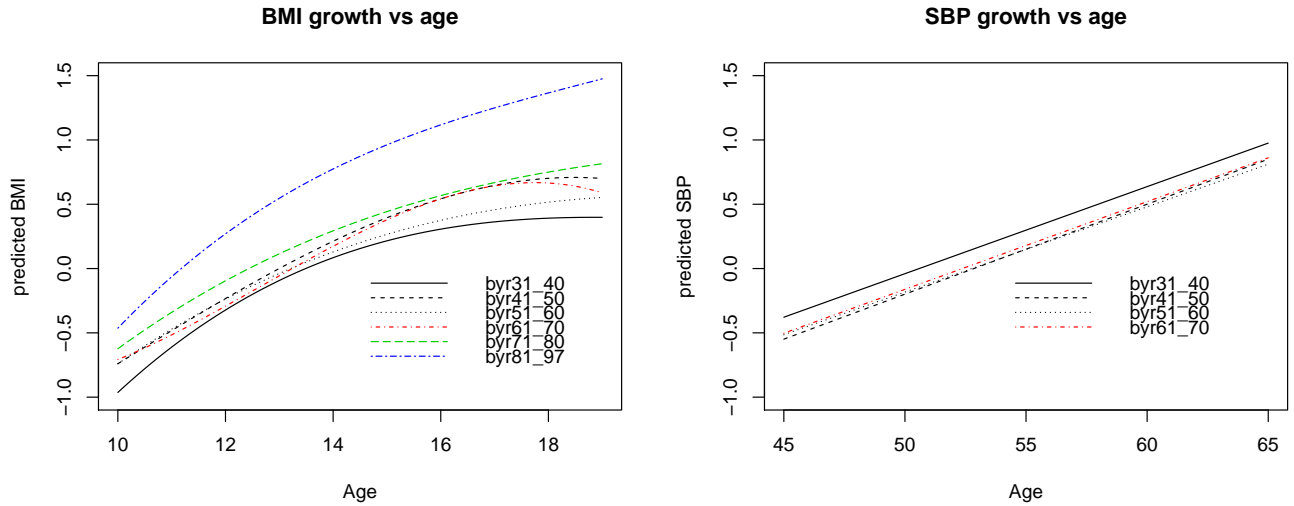


Figure 2: Predicted growth in adolescent BMI and middle-age SBP controlling for onset and historical time of a visit.

Table 3: Estimates (standard errors) of $f(Y_{2j})$, $f(C_{tj}|Y'_{2j})$ and $f(R_{ij}|\beta'_{Cj}, Y'_{2j})$.

Covariates	$f(Y_{2j})$		$f(C_{tj} Y'_{2j})$		Covariates	$f(R_{ij} \beta'_{Cj}, Y'_{2j})$	
1	-0.53	(0.11) ⁺⁺	0.67	(0.08) ⁺⁺	1	0.03	(0.11)
byr_20	1.74	(0.56) ⁺⁺	-3.12	(9.80)	byr_20	0.47	(0.36)
byr21_30	0.40	(0.27)	-0.45	(0.38)	byr21_30	0.43	(0.29)
byr31_40	0.15	(0.16)	-0.66	(0.17) ⁺⁺	byr31_40	0.16	(0.19)
byr41_50	0.32	(0.16)	-0.44	(0.21) ⁺	byr41_50	-0.03	(0.14)
byr51_60	0.49	(0.14) ⁺⁺	-0.48	(0.16) ⁺⁺	β_{C0j}	0.10	(0.21)
byr61_70	0.52	(0.15) ⁺⁺	-0.39	(0.15) ⁺⁺	β_{C1j}	0.78	(2.29)
byr71_80	0.18	(0.16)	-0.43	(0.19) ⁺	β_{C2j}	0.54	(6.95)
Y_{2j}			-0.39	(0.05) ⁺⁺	β_{C3j}	8.99	(68.2)
a_{tj}			0.20	(0.02) ⁺⁺	Y_{2j}	0.01	(0.10)
a_{tj} byr_20			4.85	(11.7)	a_{ij}	0.05	(0.01) ⁺⁺
a_{tj} byr21_30			-0.04	(0.08)	$a_{ij}\beta_{C0j}$	-0.01	(0.02)
a_{tj} byr31_40			-0.06	(0.03) ⁺	$a_{ij}\beta_{C1j}$	0.18	(0.16)
a_{tj} byr41_50			-0.01	(0.03)	$a_{ij}\beta_{C2j}$	0.21	(0.96)
a_{tj} byr51_60			-0.06	(0.03) ⁺	$a_{ij}\beta_{C3j}$	2.58	(5.02)
a_{tj} byr61_70			0.00	(0.03)	$a_{ij}Y_{2j}$	-0.01	(0.01)
a_{tj} byr71_80			-0.04	(0.03)	onset	-0.00	(0.15)
$a_{tj}Y_{2j}$			0.03	(0.01) ⁺⁺	vyr42_60	-0.33	(0.78)
a_{tj}^2			-0.02	(0.00) ⁺⁺	vyr61_70	-0.58	(0.32)
a_{tj}^2 byr_20			-2.36	(4.18)	vyr71_80	-0.05	(0.25)
a_{tj}^2 byr21_30			-0.005	(0.02)	vyr81_90	-0.26	(0.16)
a_{tj}^2 byr31_40			-0.004	(0.01)			
a_{tj}^2 byr41_50			0.001	(0.01)			
a_{tj}^2 byr51_60			0.002	(0.01)			
a_{tj}^2 byr61_70			-0.001	(0.01)			
a_{tj}^2 byr71_80			0.004	(0.01)			
$a_{tj}^2Y_{2j}$			0.004	(0.002) ⁺			
a_{tj}^3			0.000	(0.001)			
a_{tj}^3 byr_20			0.330	(0.470)			
a_{tj}^3 byr21_30			-0.003	(0.005)			
a_{tj}^3 byr31_40			-0.000	(0.002)			
a_{tj}^3 byr41_50			-0.002	(0.002)			
a_{tj}^3 byr51_60			0.000	(0.002)			
a_{tj}^3 byr61_70			-0.003	(0.002)			
a_{tj}^3 byr71_80			-0.000	(0.002)			
$a_{tj}^3Y_{2j}$			-0.002	(0.001) ⁺⁺			
onset			-0.10	(0.15)			
vyr30_40			0.02	(0.17)			
vyr41_50			0.04	(0.11)			
vyr51_60			0.05	(0.09)			
vyr61_70			-0.01	(0.07)			
vyr71_80			0.00	(0.07)			
vyr81_90			0.03	(0.06)			
vyr91_00			-0.04	(0.04)			
T_{22} or $var(\beta_{Cj})$	0.95	0.67	0.02	-5E-3	τ	0.51	0.02
				4E-4*			
				0.02 -7E-4			0.001
				-7E-4			
				6E-4			
				7E-5			
				4E-5			
σ_{CC}				0.036	σ_{RR}		0.401

+ p-value < .05; ++ p-value < .01; * $x E - y = x \times 10^{-y}$

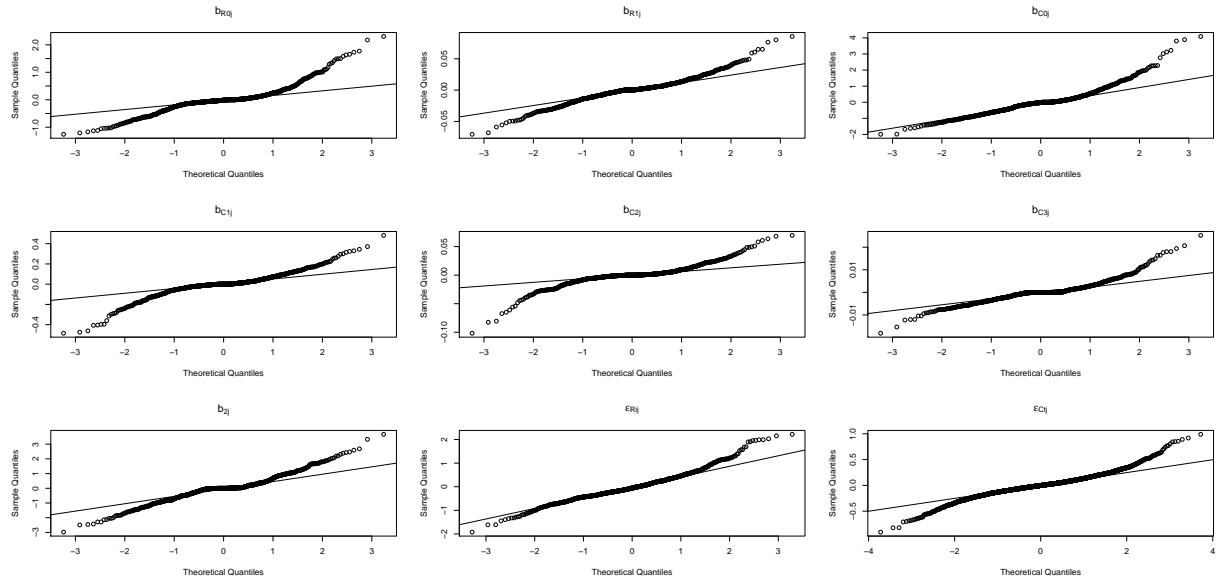


Figure 3: Residual plots of the joint model that produced estimates in Table 3.